Prenatal Diagnosis and Genetic Counseling for Mosaic Trisomy 13

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SUMMARY

Counseling parents of a fetus with trisomy 13 mosaicism remains difficult because of the phenotypic variability associated with the condition; some patients exhibit the typical phenotype of complete trisomy 13 with neonatal death, while others have few dysmorphic features and prolonged survival. This article provides a comprehensive review of the prenatal diagnosis and genetic counseling for mosaic trisomy 13, including confined placental mosaicism 13, mosaic trisomy 13 diagnosed at amniocentesis, and phylloid hypomelanosis in association with mosaic trisomy 13. [*Taiwan J Obstet Gynecol* 2010;49(1):13–22]

Key Words: confined placental mosaicism, mosaicism, phylloid hypomelanosis, prenatal diagnosis, trisomy 13

Introduction

Counseling parents of a fetus with trisomy 13 mosaicism remains difficult because of the phenotypic variability associated with the condition; some patients exhibit the typical phenotype of complete trisomy 13 with neonatal death, while others have few dysmorphic features and prolonged survival. This article provides a comprehensive review of the prenatal diagnosis and genetic counseling for mosaic trisomy 13, including confined placental mosaicism (CPM)13, mosaic trisomy 13 diagnosed at amniocentesis, and phylloid hypomelanosis in association with mosaic trisomy 13.

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Accepted: September 29, 2009

Confined Placental Mosaicism 13

CPM occurs when there is a cytogenetic discrepancy between the extraembryonic and embryonic tissues. True chromosome mosaicism appears in both placental and fetal cells, whereas CPM appears only in the placenta. [1]. CPM has been detected in 2% of viable pregnancies at 10–12 weeks' gestation [1–3]. Kalousek et al [4,5] suggested the existence of three types of CPM: (1) type I CPM with mosaic or nonmosaic aneuploidy in the cytotrophoblasts, normal diploidy in the chorionic stroma and normal diploidy in the embryonic/fetal tissues; (2) type II CPM with normal diploidy in the cytotrophoblasts, mosaic or nonmosaic aneuploidy in the chorionic stroma and normal diploidy in the embryonic/fetal tissues; and (3) type III CPM with mosaic or nonmosaic aneuploidy in the cytotrophoblasts, mosaic or nonmosaic aneuploidy in the chorionic stroma and normal diploidy in the embryonic/fetal tissues.

CPM can affect placental function and has been reportedly associated with a significant increase in perinatal loss, spontaneous abortion, and intrauterine growth restriction [5–9]. Robinson et al [10] found that meiotic origin of the extra chromosome in the placenta was highly correlated with type III CPM and an increased risk of pregnancy complications, whereas mitotic origin was highly correlated with types I and II CPM and a lower risk of pregnancy complications.

In a United States collaborative study on chorionic villus sampling (CVS), Ledbetter et al [2] found 13 cases of mosaic trisomy 13 among 11,473 cases of CVS. Nine were identified from direct preparations only and the other four from cultures only. Among these 13 cases, nine were considered to be CPM13 with normal pregnancy outcomes, and the other four were terminated with undetermined cytogenetic interpretations. Smidt-Jensen et al [11] reported one case of CPM13 with normal outcome among 2,928 CVS samples. In a study of 2,612 consecutive cases of CVS, Wang et al [8] found CPM in 51 cases (1.9%) of which trisomies 2, 7, 8 and 13, and sex chromosome abnormalities were the most frequently encountered aneuploidies. These included two cases of trisomy 13 type I CPM and one case of trisomy 13 type III CPM. Fryburg et al [12] reported one case of true mosaic trisomy 13 detected by CVS among 20 cases of true mosaicism in 1,724 CVS procedures. Pittalis et al [13] reported three cases of CPM13 with normal outcomes among 4,860 cases of CVS. Roland et al [14] reported one case of CPM13 with normal pregnancy outcome among 27 cases of CPM identified in 3,258 CVS procedures. Wang et al [15] reported five cases of mosaic trisomy 13 among 4,000 consecutive cases of CVS. In three of these cases, the trisomy 13 cell line was detected in direct preparations but not by culture, and the fetal outcomes were normal. The fourth case had mosaicism for i(13q) also identified in direct preparations but not by culture, and a normal karyotype was recorded at follow-up amniocentesis. The fifth case had mosaicism for trisomy 13 and trisomy 7 and were identified in direct preparations and culture, but not at follow-up amniocentesis. In a major review by the European Collaborative Research on Mosaicism in CVS reported by Hahnemann and Vejerslev [16], 15 cases of mosaic trisomy 13 were identified from 92,246 CVS procedures. CPM13 was found in 13 cases and true fetal mosaicism in two cases. Delatycki et al [17] reported two cases of CPM13. In the first case, trisomy 13 was identified in all 10 cells examined in short-term CVS culture and in 15 cells in long-term CVS culture, as well as in 30 of 35 cells in additional long-term CVS culture. The pregnancy was terminated, but the fetal skin fibroblasts revealed a normal karyotype in 50 cells. In the second case, trisomy was identified in 9 of 30 cells in long-term CVS culture. Follow-up amniocentesis revealed a normal karyotype; the results of ultrasound were normal, and a normal baby was born at term. Los et al [18] reported three cases of CPM13 out of 3,499 semi-direct chorionic villus preparations with low mosaicism for trisomy 13, such as 47,XY,+13[3]/46,XY[27], 47,XX,+13[2]/46,XX[28] and 47,XY,+13[2]/46,XY[28], respectively. The karyotypes were normal at amniocentesis, and the pregnancy outcomes were also normal in all these cases. In a study of 6,820 CVS cases, Schuring-Blom et al [19] found one false-positive result out of 13 cases of full trisomy 13 in cytotrophoblasts and two false-positives in three cases of mosaic trisomy 13 in cytotrophoblasts. Schuring-Blom et al [19] suggested that the diagnosis of trisomy 13 in cytotrophoblasts should be confirmed in other tissues, unless fetal abnormalities were seen at ultrasound, and that follow-up amniocentesis was advisable if mosaicism was detected at CVS. In contrast, Kalousek et al [4] only detected diploid cells in the cytotrophoblasts of some pregnancies with viable trisomy 13 conceptions, and suggested that direct preparations of CVS were unreliable for the prenatal diagnosis of trisomy 13 and that long-term villus cultures should be used. Doray et al [20] reported CPM13 associated with body wall complex in a fetus. In this case, direct chromosome analysis in chorionic villi showed a 47,XY,+13[20]/46,XY[1] karyotype, while long-term chorionic villus culture, post-mortem chromosome analysis of skin fibroblasts, and fluorescence *in situ* hybridization of fetal renal and hepatic tissues revealed a 46,XY karyotype.

When the abnormal cell line comprises at least 15% of the whole sample, then quantitative fluorescence polymerase chain reaction (QF-PCR) can detect mosaicism [21]. Discrepancies between QF-PCR results from uncultured CVS samples and karyotyping results from long-term cultured CVS samples have been reported [21–26]. Most discrepancies can be attributed to mosaicism. Three such cases of CPM13 detected by QF-PCR have been described [21,26]. Donaghue et al [21] reported a difference in results between prenatal uncultured and cultured CVS samples in two cases, where uncultured villus samples revealed mosaic trisomy 13 by QF-PCR, but cultured villus samples tested by QF-PCR and/or karyotype analysis revealed normal results. Lau et al [26] reported discrepant findings between QF-PCR in uncultured CVS samples and karyotyping of long-term cultured CVS samples in one case; mosaic trisomy 13 was detected by QF-PCR and a normal karyotype was detected by karyotyping. The baby was delivered at 39 weeks of gestation with no obvious abnormalities. Lau et al [26] suggested that in case of

discrepant results, CPM should be confirmed by amniocentesis, which is able to provide a better representation of the fetal lineage.

Mosaic Trisomy 13 Diagnosed at Amniocentesis

Multiple cell lines with different chromosome constitutions may be found in amniotic fluid cell cultures. Mosaicism with a single abnormal cell (level I mosaicism) is referred as pseudomosaicism and has no clinical significance. Mosaicism in which two or more cells with the same aberration are found in a single flask/colony (level II mosaicism) is usually referred as pseudomosaicism and of *in vitro* clonal origin. However, a true fetal chromosomal abnormality may exist in ≤1% of cases with level II mosaicism [2,12,27–29]. Mosaicism with two or more cells with the same aberration found in multiple flasks/colonies (level III mosaicism) is usually referred as true fetal mosaicism or simply as mosaicism [27,30,31].

In a study of chromosome mosaicism in 6,000 amniocentesis samples, Wilson et al [32] found level II mosaicism in 0.92% of amniocenteses and level III mosaicism in 0.2%. In a study of chromosome mosaicism in 22,000 amniocenteses, Hsu et al [33] found true chromosome mosaicism in 50 cases (0.27%), including two cases of mosaic trisomy 13. Hsu et al [34] found chromosome mosaicism in 555 of 179,663 amniocenteses (0.3%). Robinson et al [35] found that the majority of cases of mosaic trisomy 13 were associated with trisomic fertilization compatible with a meiotic origin of the extra chromosome and with postzygotic loss of one chromosome.

Hsu et al [33] and Hsu and Benn [36] recommended guidelines for the management of cases with suspected amniocyte mosaicism. Suspected amniocyte mosaicism for trisomy 13 in a single cell (single flask), multiple cells (single flask), single colony (single dish) or multiple colonies (single dish) requires extensive work-up. In the case of the flask method, this includes examination of 10 additional cells from the second flask where the first 10 cells shows only normal chromosomes, and analysis of 20 cells from a third primary culture [33]. Work-up for the *in situ* method includes examination of a total of 24 colonies from multiple *in situ* culture vessels, not including the number of colonies from the initial culture dish in which an abnormal colony or several abnormal colonies were detected [33]. Since there is considerable diversity in the clinical features of fetuses diagnosed with mosaic trisomy 13 at amniocentesis, high-resolution ultrasonography is very helpful for guiding the genetic counseling of women who elect to continue an affected pregnancy. Confirmatory cytogenetic analyses, such as repeat amniocentesis, placental analysis, cord blood sampling and analysis of cord fibroblasts, may also be helpful.

Malin et al [37] reported one case of level I mosaic trisomy 13 and two cases of level II mosaic trisomy 13 diagnosed by amniocentesis, each of which had a normal outcome and a normal karyotype after birth. Fejgin et al [38] reported prenatal diagnosis of mosaic trisomy 13 in a fetus in which trisomy 13 was detected in 4 of 10 amniocytes (40%) and 1 of 160 cord blood lymphocytes. Ultrasonography revealed an apparently normal fetus, but the pregnancy was terminated electively. The abortus had a normal phenotype, and cytogenetic analysis of the kidney, diaphragm, lung, blood from the heart, skin and placenta revealed a normal karyotype. In a major review of autosomal trisomy mosaicism diagnosed in amniocytes, Hsu et al [33] documented 15 cases of mosaic trisomy 13, and five of the 11 cases were known to have abnormal phenotypes. Delatycki and Gardner [47] reported two cases of prenatally diagnosed low-level trisomy 13 mosaicism with normal outcomes. In the first of these cases, amniocentesis revealed level II mosaicism of 47,XX,+13/47,XX,+22/46,XX with one *in situ* culture showing 46,XX in all cells, one dispersed culture showing 47,XX,+13 in 7 of 50 cells, and one dispersed culture showing 47,XX,+22 in 5 of 50 cells. Subsequent fetal blood sampling revealed a 46,XX karyotype in 100 of 100 lymphocytes. A normal baby was delivered with no dysmorphic features except for an atrial septal defect. A cord blood sample at birth showed 47,XX,+13 in 3 of 100 lymphocytes. The child was entirely normal at age 3 years 6 months. In the second case, CVS revealed trisomy 13 in 7 of 20 cells in long-term culture and in 33 of 50 cells in the second culture. Follow-up amniocentesis revealed trisomy 13 in 1 of 28 colonies in an *in situ* study and in 1 of 400 lymphocytes at cordocentesis. A normal baby was delivered and postnatal cord blood sampling revealed trisomy 13 in 1 of 150 lymphocytes, 2 of 32 amnion cells, 0 of 27 smooth chorion cells, 1 of 30 cord insertion villi cells, and 3 of 30 placental margin villus cells. The child was normal at age 17 months. Delatycki et al [17] also reported two cases of level II mosaic trisomy 13 diagnosed at amniocentesis, each of which had a normal outcome and a normal karyotype after birth. Eubanks et al [39] reported prenatal diagnosis of mosaic trisomy 13 based on second-trimester amniocyte cultures in which nine colonies (68%) had a 47,XX,+13 karyotype and six colonies (32%) had a 46,XX karyotype. Prenatal ultrasound was normal, and postmortem examination was also normal, with the exception of a

small ventricular septal defect and low-set ears. Chromosomal studies from two cultures of fetal pericardium confirmed mosaic trisomy 13 with trisomy 13 in 2 of 10 cells (20%). Wallerstein et al [40] documented an abnormal outcome in 10 of 25 cases of mosaic trisomy 13 diagnosed by amniocentesis (40%). The 10 abnormal cases were abortuses including five with multiple congenital anomalies, two with intrauterine growth restriction, and three with intrauterine death (one with a congenital heart defect and one with hydrops). They found that in 15 cases with < 50% trisomy 13 cells, there was a 26.7% (4/15) risk of abnormalities, whereas in 10 cases with > 50% trisomy 13 cells, there was a 60% (6/10) risk of abnormalities. They also found that in cases with an abnormal outcome, the mean percentage of trisomy 13 amniocytes was 58% (range, 6–94%), whereas in cases with a normal liveborn, the mean percentage of trisomy 13 amniocytes was 9.3% (range, 5–13%). Phelan et al [41] reported second-trimester diagnosis of mosaicism for trisomy 13 and triploidy in amniocyte cultures, of which 12 of 16 colonies from *in situ* culture were trisomy 13, and 4 of 16 colonies were triploid. The fetus had multiple congenital anomalies including intrauterine growth restriction, syndactyly, polydactyly, facial dysmorphism, and a scalp defect. The mosaicism was postnatally confirmed in cord blood, skin, and placenta. Chen et al [42] reported second-trimester diagnosis of mosaicism for trisomy 13 by amniocentesis in a case where mosaic trisomy 13 was detected in two separate amniocyte cultures with mosaicism for trisomy 13 in 5 of 16 (31.3%) and 3 of 20 cells (15%), respectively. Ultrasonography revealed an apparently normal fetus, but the fetus was terminated electively. The abortus had a normal phenotype. Polymorphic DNA marker analysis confirmed mosaic trisomy 13 in the samples of cord blood and umbilical cord, and trisomy 13 in the samples of placenta. Chen et al [43] also reported postnatal cytogenetic diagnosis of mosaicism for trisomy 13 in a fetus with holoprosencephaly and cystic hygroma. In that case, trisomy 13 was detected in 17 of 40 chorionic villus cells (42.5%), and polymorphic DNA marker analysis of the samples of fetal skin and placenta confirmed mosaic trisomy 13.

However, even pregnancies with a high percentage of trisomy 13 cells detected at amniocentesis may result in a relatively mild phenotype [44], or even a normal outcome [45]. Chen et al [44] reported an unusual case of mosaic trisomy 13 with a high percentage of trisomy 13 cells at amniocentesis but with relatively mild phenotypic abnormalities at birth. In that case, CVS showed a 46,XX,der(13;13)(q10;q10) karyotype. Subsequent amniocentesis and cordocentesis showed mosaic trisomy 13 with a 46,XX,der(13;13)(q10;q10)[24]/46,XX[7] karyotype on the first amniocyte culture, a 46,XX,der(13;13) (q10;q10)[36]/46,XX[10] karyotype on the second amniocyte culture, and a 46,XX,der(13;13)(q10;q10)[14]/46,XX[86] karyotype on fetal cord blood culture. The percentages of trisomy 13 cells in the blood lymphocytes at birth, 2 days old, 1 month old and 6 months old were 54%, 14%, 0% and 0%, respectively. Cytogenetic analysis of skin and cardiac tissue at 6 months revealed a normal karyotype. The baby had only a few structural abnormalities, including low-set ears, absence of the 12th rib, and a ventricular septal defect. Development was normal at the age of 8 months. Di Giacomo et al [45] additionally reported prenatal diagnosis of mosaic trisomy 13 with a high percentage of trisomy 13 cells and a normal outcome. In their case, second-trimester amniocentesis showed trisomy 13 in 24 of 34 amniocyte clones (70.6%). Subsequent cord blood sampling and CVS showed trisomy 13 cells in 10 of 100 blood lymphocytes (10%), and in 11 of 11 cells in short-term culture (100%) and in 13 of 13 in long-term culture of CVS (100%). Neonatal cord blood analysis revealed a 47,XX,+13[11]/46,XX[96] karyotype, and peripheral blood analysis at 2 years of age revealed a 47,XX,+13[18]/46,XX[96] karyotype. Examination of buccal mucosal cells, skin fibroblasts and urinary tract cells using interphase fluorescence *in situ* hybridization revealed that the percentages of cells with three chromosome 13 signals were 0% (0 of 103 cells), 5% (29 of 575 cells) and 23% (13 of 56 cells), respectively. The child was normal with no dysmorphic features at age of 2 years.

Mosaic trisomy 13 has rarely been recognized. Magenis et al [46] proposed that mosaic trisomy 13 occurs in only 5% of all trisomy 13 cases. Patients with mosaic trisomy 13 usually have a longer survival and a less severe phenotype, with a wide variation from essentially normal to grossly abnormal, according to the tissue distribution of the trisomy 13 cells [47,48]. The percentage of abnormal cells decreases with age, possibly because of natural selection against the trisomy 13 cells [44,47,49]. Individuals with mosaic trisomy 13 and an essentially normal phenotype may be fertile, and should be aware of the theoretical risk of gonadal mosaicism and the production of offspring with nonmosaic trisomy 13. In a literature review of 49 published cases, Griffith et al [50] found phenotypic variability in trisomy 13 mosaicism, with some patients having the typical phenotype of complete trisomy 13 with neonatal death and others having few dysmorphic features and prolonged survival, thus making its clinical diagnosis difficult. Griffith et al [50] also found that there was no clear correlation between the percentage

Table. Cytogenetic findings and clinical outcomes of reported cases with true mosaic trisomy 13 diagnosed by amniocentesis

Case	Indication	CVS	Amniocentesis	Cordocentesis	Phenotypic outcome	Postnatal confirmatory studies
Fejgin et al [38]	AMA	–	T13: 4/10 colonies	T13: 1/160 cells	Normal abortus	Normal: 25/25 cells (kidney, diaphragm, lung, cardiac blood, skin and placenta)
Delatycki and Gardner [47]						
Case 1	AMA	–	T13: 7/50 cells in one dispersed culture T22: 5/50 cells in one dispersed culture	Normal: 100/100 cells	Normal child at age 3 years 6 months with ASD	T13: 3/100 cells (cord blood)
Case 2	AMA	T13: 7/20 cells (1st culture) T13: 33/50 cells (2nd culture)	T13: 1/28 colonies	T13: 1/400 cells	Normal baby at age 17 months	T13:1/150 cells (cord blood) T13: 2/32 cells (amnion) T13: 0/27 cells (smooth chorion) T13: 1/30 cells (cord insertion villi) T13: 3/30 cells (placental margin villi)
Eubanks et al [39]	T21 risk=1/27	–	T13: 9/15 colonies	–	Abortus with no anatomic abnormalities except VSD and low-set ears	T13: 2/10 cells (pericardium)
Wallerstein et al [40]						
Case 1	AMA	–	T13: 33% of 33 cells T13: 3% of 39 cells (repeat)	–	Normal abortus	–
Case 2	AMA	–	T13: 57% of 30 cells	–	Normal abortus	T13: 1% of 100 cells (fetal tissue)
Case 3	AMA	–	T13: 24% of 62 cells	–	Normal abortus	T13: 28% of 50 cells (placenta)
Case 4	AMA	–	T13: 45% of 44 cells	–	Normal abortus	T13: 30% of 10 cells (placenta)
Case 5	Anxiety	–	T13: 90% of 91 cells T13: 0% (repeat)	–	Normal liveborn	–

Table. *(continued)*

Case	Indication	CVS	Amniocentesis	Cordocentesis	Phenotypic outcome	Postnatal confirmatory studies
Case 6	AMA	–	T13: 10% of 29 cells T13: 0% of 38 cells (repeat)	–	Normal liveborn	–
Case 7	AMA	–	T13: 10% of 39 cells	–	Normal child at age 1 year	T13: 0% of 30 cells (foreskin)
Case 8	AMA	–	T13: 7% of 31 cells	–	Normal abortus	–
Case 9	Anxiety	–	T13: 21% of 23 cells	–	Normal abortus	–
Case 10	AMA	–	T13: 7% of 60 cells	–	Normal liveborn	–
Case 11	Anxiety	–	T13: 36% of 55 cells	–	Normal abortus	–
Case 12	AMA	–	T13: 68% of 44 cells	–	Normal abortus	–
Case 13	AMA	–	T13: 82% of 24 cells	–	Normal abortus	–
Case 14	AMA	–	T13: 42% of 35 cells	–	Normal abortus	–
Case 15	AMA	–	T13: 59% of 20 cells	–	Normal abortus	–
Case 16	AMA	–	T13: 52% of 25 cells	–	Abnormal abortus, IUFD	T13: 6% of 20 cells (placenta)
Case 17	Anxiety	–	T13: 25% of 32 cells T13: 8% of 20 cells (repeat)	–	Abnormal abortus, MCA	–
Case 18	AMA	–	T13: 12% of 66 cells T13: 0% of 100 cells (repeat)	–	Abnormal abortus, MCA	T13: 11% of 36 cells (fetal tissue)
Case 19	AMA	–	T13: 89% of 19 cells	–	Abnormal abortus, hydrops	–
Case 20	AMA	–	T13: 61% of 44 cells	–	Abnormal abortus, MCA	–
Case 21	AMA	–	T13: 96% of 60 cells	–	Abnormal abortus, IUFD	–
Case 22	AMA	–	T13: 10% of 42 cells	–	Abnormal abortus, MCA	–
Case 23	AMA	–	T13: 57% of 18 cells	–	Abnormal abortus, MCA	–
Case 24	AMA	–	T13: 50% of 30 cells	–	Abnormal abortus, MCA	–
Case 25	AMA	–	T13: 18% of 55 cells	–	Abnormal abortus, IUFD	–

Phelan et al [41]	Fetal abnormalities	–	T13: 12/16 colonies Triploidy: 4/16 colonies	–	Abnormal baby with IUGR, syndactyly, polydactyly, scalp defect, low-set ears, small jaw, cleft palate	T13: 16/20 cells (cord blood) Triploidy: 4/20 cells (cord blood) T13: 7/25 cells (skin fibroblasts) Triploidy: 18/25 cells (skin fibroblasts) Triploidy: 32/32 cells (amnion) T13: 15/15 cells (chorion villi)
Chen et al [44]	Pompe disease	T13: 30/30 cells	T13: 24/30 colonies (1^{st}) T13: 36/46 colonies (2^{nd})	T13: 14/100 cells	Mild abnormalities of low-set ears, absence of the 12^{th} rib and VSD. Normal development at age 8 months	T13: 27/50 cells (cord blood) (at birth) T13: 7/50 cells (peripheral blood) (age 2 days) T13: 0/21 cells (peripheral blood) (age 1 month) T13: 0/100 cells (peripheral blood) (age 6 months) T13: 0/100 cells (skin fibroblasts) (age 6 months) T13: 0/100 cells (cardiac tissue) (age 6 months)
Di Giacomo et al [45]	AMA	T13: 11/11 cells (short-term) T13: 11/11 cells (long-term)	T13: 24/34 colonies	T13: 10/100 cells	Normal child at age 2 years	T13: 11/107 cells (cord blood) (at birth) T13: 18/114 cells (peripheral blood) (age 2 years) T13 signals (FISH): 0/103 cells (buccal mucosal cells) T13 signals (FISH): 29/575 cells (skin fibroblasts) T13 signals (FISH): 13/56 cells (urinary tract cells)
Chen et al [42]	Abnormal maternal serum screening	–	T13: 5/16 colonies (1^{st}) T13: 3/20 colonies (2^{nd})	–	Normal abortus	T13: chromosome 13 gene dosage increased about 30% in cord blood, 20% in umbilical cord and 100% in placenta by QF-PCR

CVS = chorionic villi sampling; AMA = advanced maternal age; – = no analysis; T13 = trisomy 13; ASD = atrial septal defect; VSD = ventricular septal defect; IUFD = intrauterine fetal death; MCA = multiple congenital anomalies; IUGR = intrauterine growth restriction; FISH = fluorescence in situ hybridization; QF-PCR = quantitative fluorescent polymerase chain reaction.

of trisomy 13 cells and the level of intellectual function, and that the most commonly associated malformations were ear anomalies, cleft lip and palate, and congenital heart defects.

The Table summarizes the clinical details of reported cases of mosaic trisomy 13 diagnosed by amniocentesis. The spectrum of phenotypic variations in cases with prenatally detected mosaic trisomy 13 is broad. Therefore, genetic counseling of parents of fetuses with prenatally detected mosaic trisomy 13 remains difficult and further studies are needed to identify the indicators associated with favorable outcome.

Mosaic Trisomy 13 and Phylloid Hypomelanosis

Phylloid hypomelanosis is a distinct form of pigmentary mosaicism characterized by hypochromic lesions with various elements, including round or oval patches and oblong macules arranged in such a way as to resemble the leaves of a begonia (Greek *phyllom* = leaf, *eidos* = form) [51]. Phylloid hypomelanosis is known to be associated with mosaic trisomy 13 [52–57]. In a review of six cases of phylloid hypomelanosis, Happle [54] reported that five had mosaic trisomy 13 and that skin fibroblasts showed chromosome mosaicism in four out of these five patients. Happle [54] suggested that phylloid hypomelanosis mainly originates from a mosaic state involving chromosome 13. González-Enseñat et al [58] reported mosaic partial trisomy 13 in two girls with mental deficiency and phylloid hypomelanosis. One patient showed mental deficiency, phylloid hypomelanosis, syndactyly, clinodactyly, trichomegaly of the eyelashes, low frontal hairline and several pale pink telangiectatic macules, while her blood lymphocytes showed a 46,XX karyotype, and fibroblasts derived from the lesional skin demonstrated tetrasomy of 13q21–qter. The second patient showed mental deficiency, phylloid hypomelanosis, epileptic seizures, dental malposition, oligodontia, preauricular fistulas, scoliosis, tethered cord, and syringomyelia. Her blood lymphocytes showed a 46,XX karyotype, and fibroblasts derived from the lesional skin demonstrated trisomy of 13q22–qter. González-Enseñat et al [58] suggested that phylloid hypomelanosis is a distinct clinicogenetic entity that is most likely related to the 13q region. Dhar et al [59] reported an 8-year-old girl with phylloid hypomelanosis and precocious puberty. The girl was found to have mosaicism for tetrasomy 13q in the form of inverted dup(13)(q21) in skin fibroblasts and peripheral blood lymphocytes. Dhar et al [59] suggested that mosaic overexpression of the candidate pigmentary genes such as endothelin receptor type B (*EDNRB*), which is responsible for melanoblast migration, may cause impaired melanoblast migration and melanocyte formation, leading to phylloid hypomelanosis and depigmentation.

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